## ORIGINAL RESEARCH

# Association of Rosacea With Cardiovascular Disease: A Retrospective Cohort Study

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**BACKGROUND:** There is emerging evidence that rosacea, a chronic cutaneous inflammatory disease, is associated with various systemic diseases. However, its association with cardiovascular disease (CVD) remains controversial. We aimed to investigate whether patients with rosacea are at increased risk of developing CVD.

**METHODS AND RESULTS:** This retrospective cohort study from the Korean National Health Insurance Service-Health Screening Cohort included patients with newly diagnosed rosacea (n=2681) and age-, sex-, and index year–matched reference populations without rosacea (n=26 810) between 2003 and 2014. The primary outcome was subsequent CVD including coronary heart disease and stroke. Multivariable Cox regression analyses were used to evaluate adjusted hazard ratios for subsequent CVD adjusted for major risk factors of CVD. Compared with the reference population (13 410 women; mean [SD] age, 57.7 [9.2] years), patients with rosacea (1341 women; mean [SD] age, 57.7 [9.2] years) displayed an increased risk for CVD (adjusted hazard ratios, 1.20; 95% CI, 1.03–1.40) and coronary heart disease (adjusted hazard ratios, 1.29; 95% CI, 1.05–1.60). The risk for stroke was not significantly elevated (adjusted hazard ratios, 1.12; 95% CI, 0.91–1.37).

**CONCLUSIONS:** This study suggests that patients with rosacea are more likely to develop subsequent CVD. Proper education for patients with rosacea to manage other modifiable risk factors of CVD along with rosacea is needed.

**Key Words:** cardiovascular diseases ■ coronary heart disease ■ inflammation ■ rosacea ■ stroke

Rosacea is a chronic relapsing inflammatory skin disease characterized by erythema, flushing, telangiectasia, papules, and pustules primarily on the central part of the face,[1] commonly affecting middle-aged women.[2–4] It is well known for its high prevalence among the fair-skinned population, ranging from 2% to 22%.[5] Notably, it is also frequently found in people with darker skin as well, with a reported prevalence up to 10%.[6] In South Korea, according to outpatient-based research, 1.21% of 47 947 first-visit outpatients had rosacea.[4] The pathogenesis of rosacea is not fully understood yet; however, environmental factors, genetic factors, immune dysregulation, neurogenic inflammation, and microorganisms have

been presumed to play a role in the development of rosacea.[7,8] Risk factors for rosacea are ultraviolet light exposure, past smoking, alcohol consumption, high body mass index, and psychological stress.[9]

Rosacea was formerly considered to be a disease limited to the skin; however, a growing number of studies have reported an association with metabolic disease, gastrointestinal disease, neurologic disease, and psychiatric disease, suggesting the systemic impact of rosacea.[9] Cardiovascular disease (CVD), the leading cause of morbidity and mortality worldwide, accounts for 1 in every 5 deaths in South Korea.[10,11] It was reported that patients with rosacea were more likely to have metabolic diseases, which can put them

## CLINICAL PERSPECTIVE

### What Is New?

- Patients with rosacea are more likely to develop subsequent cardiovascular disease, compared with the reference population.

### What Are the Clinical Implications?

- Proper education for patients with rosacea to manage other modifiable risk factors of cardiovascular disease along with rosacea is needed.

### Nonstandard Abbreviations and Acronyms

**aHRs**          adjusted hazard ratios
**NHIS-HEALS**    the National Health Insurance Service-Health Screening Cohort

at higher risk for developing CVD.[8,12] Several previous studies have investigated the correlation between CVD and rosacea.[13–15] A Danish cohort study and an American case–control study showed null association between CVD and rosacea.[14,15] On the other hand, a Taiwanese cross-sectional study reported an increased risk of coronary artery disease in patients with rosacea compared with patients without rosacea.[13] However, these studies had limitations of having cross-sectional designs,[12,13] which cannot determine the causality between exposure and outcome, lacking major covariates such as drinking habits, body mass index, and physical activity[13–15] or having a too-short follow-up period.[15]

In this study, we aimed to investigate the association of rosacea with the development of subsequent CVD using data obtained from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS).

## METHODS

Following the policy of the NHIS, the data cannot be provided to other researchers or to third parties.

## Data Source

This is a retrospective cohort study using the NHIS-HEALS. The NHIS is a single-payer and the universal health care provider of South Korea and provides health insurance for ≈97% of Korean citizens.[16] The NHIS-HEALS is a population-based, 14-year cohort starting from 2002 established by the NHIS.[17] This cohort consists of 514 866 representative participants who were randomly selected, comprising 10% of those who participated in the national health screening in 2002 and 2003 provided by the NHIS and aged between 40 and 79 years, as of the end of December 2002.[17] The NHIS-HEALS provides the database of eligibility, health care use, type of health care providers, and the national health screening results that contain anthropometric measures such as height, weight and blood pressure, laboratory blood tests, and self-reported questionnaires on the individual's health behavior.[17] The NHIS provides the collected data for research purposes, and multiple epidemiologic studies using these data have demonstrated their validity.[17,18]

## Study Population

To identify newly diagnosed patients with rosacea, we excluded patients with a history of rosacea before 2003. Subsequently, we extracted patients with rosacea from 2003 to 2014, who underwent a health examination within 3 years before the date of diagnosis. The diagnosis of rosacea was defined as a hospital visit under the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes for rosacea (L71).[14,19,20] The first diagnosis date of rosacea of each study participant was defined as the index date.

The primary outcome was the development of subsequent CVD in a patient with rosacea. We excluded patients with a history of CVD at any time before the index date and the participants were followed up from their own index date until December 31, 2015, death, or diagnosis of CVD, whichever came first. The CVD events were defined as hospitalization because of the diagnosis codes pertaining to coronary heart disease (CHD) (*ICD-10* code I20–25) or stroke (*ICD-10* code I60–69).[18,21]

We randomly selected a 1:10 age-, sex-, and index year–matched reference population without rosacea and previous CVD history from the NHIS-HEALS. The index dates for the reference population were designated as the date of the health examination.

Figure 1 presents the flow diagram of the study population. We enrolled 2948 participants who were diagnosed with rosacea between 2003 and 2014 and underwent health screening within 3 years before the diagnosis of rosacea from the NHIS-HEALS. After excluding 125 participants with a history of CVD, 139 individuals with missing values for covariates, and 3 unmatched cases, we finally identified 2681 patients with rosacea and a 26 810 age-, sex-, and index year–matched reference population.

## Statistical Analysis

We performed a $\chi^2$ test for categorical variables and the ANOVA for continuous variables to evaluate the differences in the distribution of the covariates between the patients with rosacea and the reference
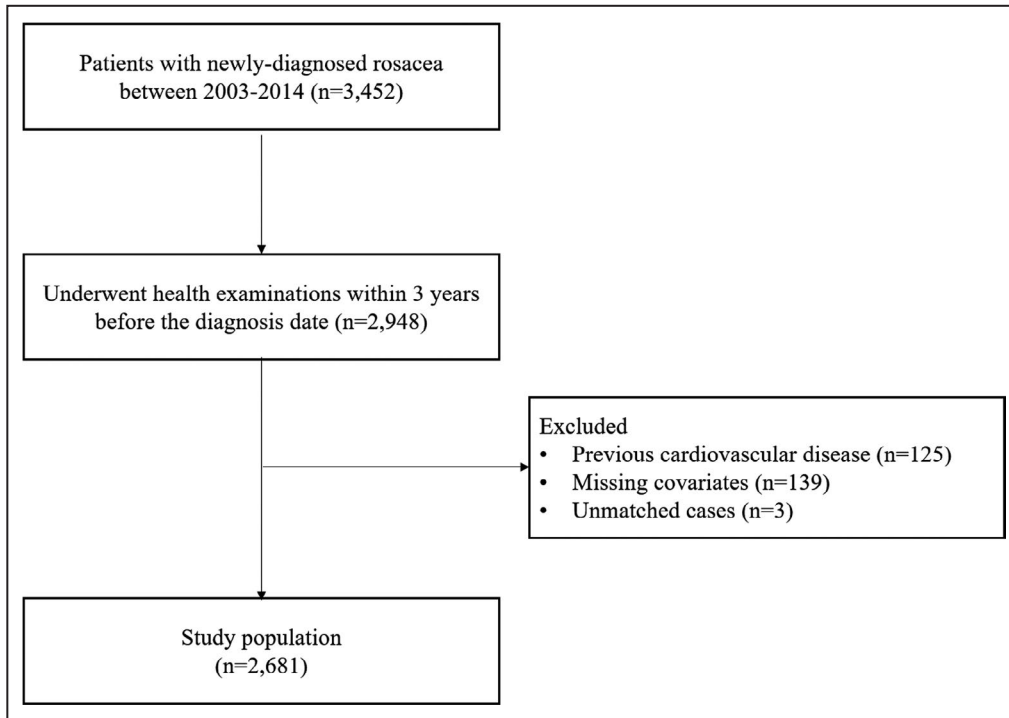
**Figure 1.  Flow diagram of the study population.**

population. Multivariable Cox proportional hazards regression analysis was performed to determine the adjusted hazard ratios (aHRs) and 95% CIs for the risk of CVD, CHD, and stroke to investigate the association between the disease and rosacea. A cumulative incidence curve for CVD was also constructed (Figure 2).
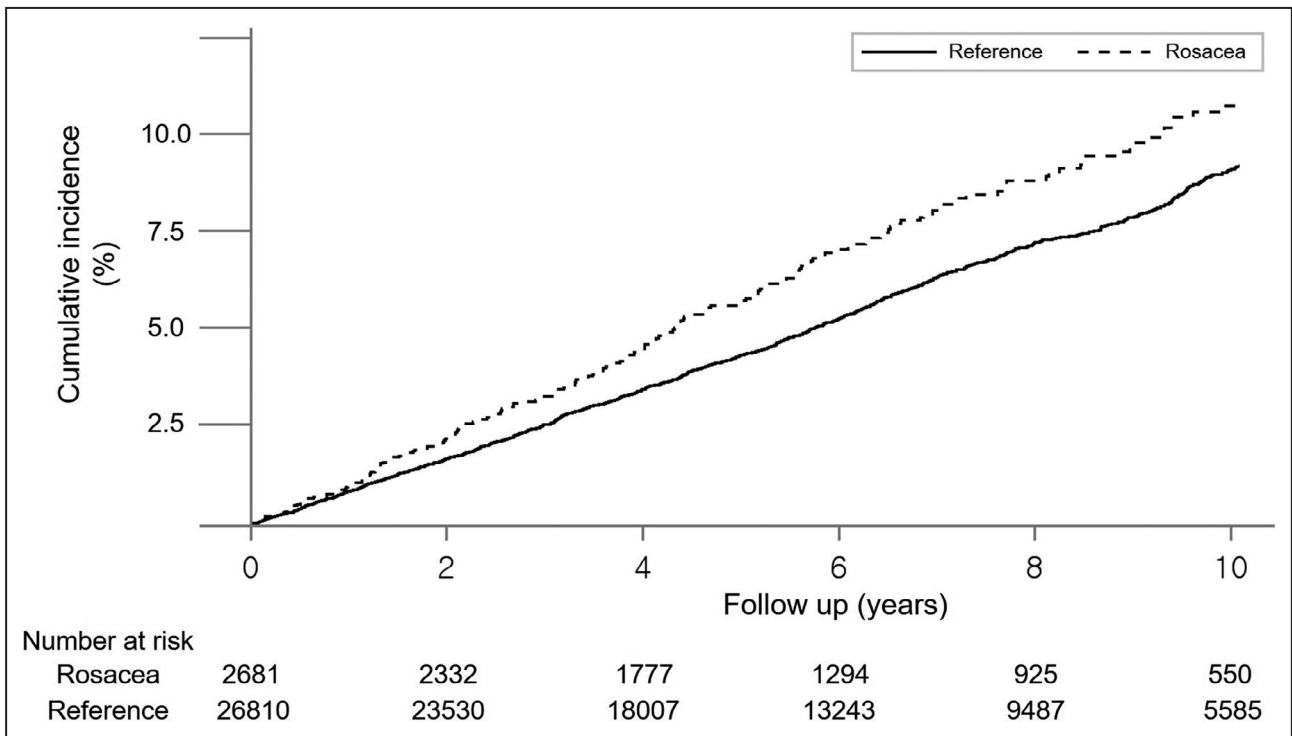


**Figure 2.  The cumulative incidence curve for cardiovascular disease.**

Predominant risk factors for CVD are smoking, alcohol consumption, low physical activity, obesity, hypertension, and diabetes.[10] We took into account risk factors of rosacea and CVD for adjustments. The considered covariates in the Cox regression were age (years), sex (men or women), household income (first, second, third, or fourth quartile), smoking status (never, past, and current smokers), alcohol intake (0, 1–2, 3–4, and ≥5 times per week), physical activity (0, 1–2, 3–4, and ≥5 times per week), body mass index (kg/m$^2$), systolic blood pressure (mm Hg), total cholesterol (mg/dL), fasting serum glucose (mg/dL), index year, and Charlson comorbidity index. Household income was

determined by the insurance premium status of the participant, and the Charlson comorbidity index was calculated using the algorithm adapted from a previous study.[22] Exercise frequency was defined based on a self-administrated questionnaire of lifestyle behaviors. We used the number of moderate (≥30 minutes per day; eg, brisk walking, tennis, bicycle riding, gardening) to vigorous (≥20 minutes per day; eg, running, aerobics, high-speed cycling, hiking) physical activities per week that participants engaged in. Supplementary analysis with additional adjustment of medication use for hypertension, diabetes, and dyslipidemia was also conducted. Stratified analyses of CVD according to

**Table 1.** Baseline Characteristics of the Study Population

| | Reference population (n=26 810) | Patients with rosacea (n=2681) | *P* value |
|---|---|---|---|
| Age, y, mean (SD) | 57.7 (9.2) | 57.7 (9.2) | |
| Sex, no. (%) | | | |
| Men | 13 400 (50.0) | 1340 (50.0) | |
| Women | 13 410 (50.0) | 1341 (50.0) | |
| Household income, quartiles, no. (%) | | | <0.001 |
| First (highest) | 8295 (30.9) | 1072 (40.0) | |
| Second | 7186 (26.8) | 744 (27.8) | |
| Third | 6195 (23.1) | 484 (18.1) | |
| Fourth (lowest) | 5134 (19.2) | 381 (14.2) | |
| Smoking, no. (%) | | | <0.001 |
| Never smoker | 18 787 (70.1) | 1902 (70.9) | |
| Past smoker | 3497 (13.0) | 412 (15.4) | |
| Current smoker | 4526 (16.9) | 367 (13.7) | |
| Physical activities, times/wk, no. (%) | | | 0.035 |
| 0 | 11 849 (44.2) | 1256 (46.9) | |
| 1–2 | 6559 (24.5) | 599 (22.3) | |
| 3–4 | 3628 (13.4) | 357 (13.3) | |
| ≥5 | 4774 (17.8) | 469 (17.5) | |
| Alcohol intake, times/wk, no. (%) | | | <0.001 |
| 0 | 16 622 (62.0) | 1809 (67.5) | |
| 1–2 | 7144 (26.7) | 550 (20.5) | |
| 3–4 | 2099 (7.8) | 210 (7.8) | |
| ≥5 | 945 (3.5) | 112 (4.2) | |
| Charlson comorbidity index, no. (%) | | | <0.001 |
| 0 | 11 462 (42.8) | 976 (36.4) | |
| 1 | 8336 (31.1) | 832 (31.0) | |
| ≥2 | 7012 (26.2) | 873 (32.6) | |
| Body mass index, mean (SD), kg/m$^2$ | 23.9 (2.9) | 23.8 (2.8) | 0.673 |
| Systolic blood pressure, mean (SD), mm Hg | 125.4 (15.8) | 124.6 (15.7) | 0.024 |
| Diastolic blood pressure, mean (SD), mm Hg | 77.8 (12.2) | 77.7 (10.5) | 0.539 |
| Fasting serum glucose, mean (SD), mg/dL | 99.7 (26.3) | 98.0 (25.8) | 0.002 |
| Total cholesterol, mean (SD), mg/dL | 199.1 (36.7) | 199.8 (38.0) | 0.379 |
| Taking hypertension medication (%) | 8240 (30.7) | 834 (31.1) | 0.690 |
| Taking diabetes medication (%) | 3711 (13.8) | 439 (16.4) | <0.001 |
| Taking dyslipidemia medication (%) | 3486 (13.0) | 465 (17.3) | <0.001 |

the subgroups of age, sex, household income, smoking status, physical activity, alcohol intake, body mass index, and Charlson comorbidity index were performed. Additionally, sensitivity analyses were performed by excluding participants who developed CVD within 1, 2, and 3 years from the index date. Lastly, propensity-matched analysis was performed to validate our results. Propensity score matching was conducted using the greedy matching method. Using a 1:1 matching ratio between the control and patients with rosacea, a caliper of 0.2 times the SD of the logit propensity score was used. Upon propensity score matching, all covariates were taken into account. All the statistical tests were 2-sided, with a P value of <0.05. Data collection and statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC). The present study was exempt from the approval of the Institutional Review Board of SMG-SNU Boramae Medical Center because the data set consisted of de-identified secondary data.

## RESULTS

Table 1 depicts the baseline characteristics of the study population. The study participants consisted of 50.0% men and 50.0% women with a mean (SD) age of 57.7 (9.2) years. Compared with the reference population, patients with rosacea were more likely to take diabetes or dyslipidemia medications, have a higher household income, smoke less, drink less, exercise less, and have additional comorbidities. There was no significant difference in the body mass index and cholesterol levels between the 2 groups. Patients with rosacea tended to have slightly lower systolic blood pressure and fasting serum glucose levels.

Among the patients with rosacea, the incidence rates per 1000 person-years with respect to CVD, CHD, and stroke were 11.44, 5.88, and 6.10, respectively, as compared with 9.36, 4.35, and 5.44 among the reference group, respectively (Table 2). Patients with rosacea had an increased risk for CVD (aHR, 1.20 [95% CI, 1.03–1.40]; P=0.017) and CHD (aHR, 1.29 [95% CI, 1.05–1.60]; P=0.017) compared with the reference group. On the other hand, there was no association observed between rosacea and stroke (aHR, 1.12 [95% CI, 0.91–1.37]; P=0.282). The unadjusted cumulative incidence curve of the CVD events is shown in Figure 2. This figure also demonstrated an increased risk for CVD in the rosacea population. Supplementary analysis with additional adjustment of medication use for hypertension, diabetes, and dyslipidemia is noted in Table S1. The result of this analysis was consistent with the major result in Table 2; patients with rosacea had increased risk for CVD (aHR, 1.24; P=0.010) and CHD (aHR, 1.36; P=0.009), but not significant for stroke (aHR, 1.13; P=0.282).

The results of the stratified analyses are shown in Table 3. Although some subgroups were not of statistical significance, the results of all the subgroups showed increased aHR and the impact of rosacea on the primary outcome was consistent across all subgroups.

In the sensitivity analyses (Table 4), although the statistical significances were attenuated upon a washout period of 2 and 3 years, the rosacea population consistently demonstrated a tendency towards an increased risk for CVD and CHD.

Propensity score matching yielded 2642 matched controls. The controls were considered as a balanced match, because all the standardized differences were <0.2 (Table S2). The result confirmed that patients with

**Table 2.** **Association of Rosacea and Cardiovascular Disease**

|  | Reference population (n=26 810) | Patients with rosacea (n=2681) | P value |
|---|---|---|---|
| Cardiovascular disease |  |  |  |
| Events | 1572 | 193 |  |
| Incidence, per 1000 person-y | 9.36 | 11.44 |  |
| aHR* (95% CI) | 1.00 (reference) | 1.20 (1.03–1.40) | 0.017 |
| Coronary heart disease |  |  |  |
| Events | 731 | 99 |  |
| Incidence, per 1000 person-y | 4.35 | 5.88 |  |
| aHR (95% CI) | 1.00 (reference) | 1.29 (1.05–1.60) | 0.017 |
| Stroke |  |  |  |
| Events | 913 | 103 |  |
| Incidence, per 1000 person-y | 5.44 | 6.10 |  |
| aHR (95% CI) | 1.00 (reference) | 1.12 (0.91–1.37) | 0.282 |

aHR indicates adjusted hazard ratio.

*Adjusted hazard ratios were calculated by Cox proportional hazards regression after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, blood pressure, total cholesterol, fasting serum glucose, year of diagnosis, and Charlson comorbidity index.

**Table 3.   Risk for Cardiovascular Disease of Patients With Rosacea Compared With the Reference Population According to Subgroups**

|  | aHR* (95% CI) | P value |
|---|---|---|
| Age, y | | |
| <60 | 1.36 (1.09–1.70) | 0.006 |
| ≥60 | 1.05 (0.85–1.29) | 0.668 |
| Sex | | |
| Men | 1.17 (0.96–1.43) | 0.111 |
| Women | 1.20 (0.95–1.52) | 0.124 |
| Income | | |
| High | 1.27 (1.05–1.53) | 0.016 |
| Low | 1.15 (0.85–1.55) | 0.369 |
| Smoking | | |
| Never or past | 1.10 (0.92–1.33) | 0.301 |
| Current | 1.37 (1.07–1.77) | 0.014 |
| Physical activity | | |
| No | 1.09 (0.88–1.34) | 0.448 |
| Yes | 1.34 (1.08–1.66) | 0.008 |
| Alcohol intake | | |
| No | 1.10 (0.92–1.33) | 0.295 |
| Yes | 1.43 (1.10–1.86) | 0.008 |
| Body mass index, kg/m$^2$ | | |
| <23 | 1.19 (0.98–1.44) | 0.080 |
| ≥23 | 1.22 (0.96–1.56) | 0.107 |
| Charlson comorbidity index | | |
| 0 | 1.05 (0.78–1.41) | 0.738 |
| ≥1 | 1.30 (1.09–1.55) | 0.004 |

aHR indicates adjusted hazard ratio.

*Adjusted hazard ratios were calculated by Cox proportional hazards regression after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, blood pressure, total cholesterol, fasting serum glucose, year of diagnosis, and Charlson comorbidity index.

rosacea had an increased risk for CVD (aHR, 1.30 [95% CI, 1.05–1.61]) compared with propensity score–matched controls (Table S3).

## DISCUSSION

In this retrospective cohort study, we observed that the patients with rosacea exhibited an increased risk for subsequent CVD and CHD, compared with the reference population after adjustments for confounders. These findings remained consistent in the subgroup and sensitivity analyses. Although the statistical significances were attenuated because of the decreased number of cases in the subgroups, the patients with rosacea consistently demonstrated a tendency of increased risk for CVD in the subgroup and sensitivity analyses. On the other hand, the risk of stroke was not increased because of rosacea, which was consistently found in previous studies.[13,14]

The association between rosacea and CVD remains controversial, although a couple of previous studies have investigated the risk of CVD in patients with rosacea.[13–15] One such study is a retrospective cohort study conducted in Denmark,[14] which reported a null association between rosacea and the subsequent CVD. Compared with our study, the population of this study was younger and fewer cases were detected, which raises the possibility of type 2 error. Moreover, they did not adjust for the major covariates of CVD, such as physical activity and body mass index. In addition, they merely adjusted for alcohol abuse, which only accounted for 2.1% of the rosacea population, instead of considering individual alcohol consumption. Lastly, the difference in ethnicity of major study participants could also be a possible reason for the different findings compared with our study.

To our knowledge, there is only 1 study among Asian populations in Taiwan.[13] This study mainly focused on the association of CVD risk factors among patients with rosacea. The study reported that rosacea was associated with hypertension, dyslipidemia, and coronary artery disease. However, this study also did not consider the major confounding variables, such as smoking, alcohol consumption, body mass index, physical activity, and socioeconomic status. Furthermore, their actual study design was cross-sectional, which cannot explain the causal relationship between rosacea and CVD.[23] Only 34.1% of the CHD cases identified in this study developed after the diagnosis of rosacea, which means that the majority of the data in the analysis consisted of CHD cases before the diagnosis of rosacea.

The last study was conducted in the United States.[15] This study reported that rosacea was not associated with CVD. However, this study was only followed up for a year and did not adjust for most of the major risk factors such as smoking, alcohol intake, physical activity, body mass index, blood pressure, and dyslipidemia, which are more prevalent among patients with rosacea.[13]

To date, previous studies that investigated the association of rosacea with CVD did not address the major confounders or temporal relationships of the 2 diseases. Furthermore, it has been less explored among the Asian population. Our study further extends the knowledge of the previous studies by demonstrating a causal relationship by considering possible confounding variables.

Increased CHD risk in patients with rosacea observed in this study raises the possibility that chronic skin inflammation induced by rosacea can lead to systemic inflammation, which is supported by several previous studies that showed patients with rosacea have significantly elevated C-reactive protein levels,[12,24,25] and are more likely to have metabolic diseases.[8,9,26] Furthermore, a positive correlation was also reported

**Table 4.  Sensitivity Analysis on the Association of Rosacea and Cardiovascular Disease**

| | Reference population | Patients with rosacea | P value |
|---|---|---|---|
| **Washout 1 y** | | | |
| Cardiovascular disease | | | |
| Events | 1335 | 165 | |
| aHR* (95% CI) | 1.00 (reference) | 1.23 (1.04–1.44) | 0.014 |
| Coronary heart disease | | | |
| Events | 615 | 83 | |
| aHR (95% CI) | 1.00 (reference) | 1.31 (1.04–1.64) | 0.023 |
| Stroke | | | |
| Events | 778 | 89 | |
| aHR (95% CI) | 1.00 (reference) | 1.15 (0.92–1.44) | 0.209 |
| **Washout 2 y** | | | |
| Cardiovascular disease | | | |
| Events | 1122 | 134 | |
| aHR (95% CI) | 1.00 (reference) | 1.19 (1.00–1.43) | 0.054 |
| Coronary heart disease | | | |
| Events | 519 | 67 | |
| aHR (95% CI) | 1.00 (reference) | 1.26 (0.97–1.62) | 0.082 |
| Stroke | | | |
| Events | 644 | 72 | |
| aHR (95% CI) | 1.00 (reference) | 1.14 (0.89–1.45) | 0.302 |
| **Washout 3 y** | | | |
| Cardiovascular disease | | | |
| Events | 922 | 109 | |
| aHR (95% CI) | 1.00 (reference) | 1.19 (0.97–1.45) | 0.091 |
| Coronary heart disease | | | |
| Events | 417 | 52 | |
| aHR (95% CI) | 1.00 (reference) | 1.22 (0.91–1.63) | 0.184 |
| Stroke | | | |
| Events | 540 | 61 | |
| aHR (95% CI) | 1.00 (reference) | 1.15 (0.88–1.51) | 0.293 |

aHR indicates adjusted hazard ratio.

*Adjusted hazard ratios were calculated by Cox proportional hazards regression after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, blood pressure, total cholesterol, fasting serum glucose, year of diagnosis, and Charlson comorbidity index.

between the severity of rosacea and cardiovascular comorbidities,[27] and decreased risk of developing atherosclerosis and CVD in patients with rosacea taking tetracyclines, which have an anti-inflammatory effect.[27,28]

Atherosclerosis, a key process in CHD, has been considered a chronic inflammatory disorder.[29,30] Although the exact pathogenesis of rosacea is still unknown, substantial similarities exist between the inflammatory pathways in rosacea and atherosclerosis.[9,31] Rosacea is histologically characterized by macrophage and mast cell infiltration and type 1 helper T/type 17 helper T polarized inflammation.[32] Cytokines from macrophage, type 1 helper T cells, and type 17 helper T cells collaborate in an interactive manner to cause skin inflammation in rosacea.[33,34] On the other hand, macrophages play a crucial role in the development and progression of plaque.[34] Type 1 helper T cells promote plaque growth and further activate macrophages,[35] and type 17 helper T cells promote intraplaque neo-angiogenesis and intraplaque hemorrhage.[35,36]

In addition to the similarity of inflammatory processes, the involvement of reactive oxygen species in the pathogenesis of both rosacea and CVD can also explain the link.[9,37,38] The vital role of reactive oxygen species has already been established in CVD, while the importance of reactive oxygen species in rosacea is gradually being revealed. Paroxonase-1, known for its antioxidant and anti-atherosclerotic effects, protects high-density lipoprotein and low-density lipoprotein from oxidation, reduces hydrogen peroxide and lipid peroxide, and hydrolyzes homocysteine thiolactone.[39] Decreased activity and concentration of paroxonase-1

in CVD and rosacea were observed when compared with the control.[37,40,41] It was also found that a high plasma malondialdehyde level, a biomarker for oxidative stress as well as a low antioxidant potential level, was detected in patients with rosacea compared with the control.[42]

Although the rosacea population had increased risk for CHD, they did not have an elevated risk for stroke in our study. Stroke is grossly divided into ischemic stroke and hemorrhagic stroke, and each has its own pathophysiology and risk factors.[43,44] Ischemic stroke shares major risk factors of atherosclerosis and is strongly associated with cardiac diseases, especially atrial fibrillation.[45] On the other hand, hemorrhagic stroke is associated with hypertensive change and vascular abnormalities.[46] Although rosacea is associated with atherosclerosis as mentioned above, its association with hypertensive change or abnormalities of cerebral vessels has not been reported. This may explain why the rosacea population showed elevated risk for CHD, but not for stroke. Given that rosacea is associated with subsequent development of CHD in our study, further research with a larger population is needed to reveal the association of ischemic stroke and transient ischemic attack with rosacea.

## Strengths and Limitations

This study has several limitations. First, the severity and type of rosacea were not considered. Since CVD can be associated with rosacea in a severity-dependent manner,[27] the severity or type should be taken into account for deriving more accurate associations. However, we analyzed the association based on a nationwide database after adjusting for various covariates and carried out subgroup and sensitivity analyses to confirm the association. In addition, types of rosacea are often mixed as the disease progresses, and the possibility that all types may be presentations of the same underlying inflammatory continuum was also raised.[1,47] Second, the operational definition of CVD may be prone to misdiagnoses, which is a common problem in studies using *ICD-10* codes to obtain data. The operational definition of CVD in this study was adopted on the basis of previous studies using similar data sources.[18,48] Third, this study may not be generalizable to people of other ethnic backgrounds. Likewise, a similar study conducted in Denmark showed results that were different from our study.[14] Therefore, additional research based on various ethnicities are required to confirm the association. Fourth, our study has an observational nature and there is a possibility that wealthier patients had more ready access to health care. However, we tried to take this into account in the analysis and conducted the stratified analysis for multiple subgroups including household income. The result of subgroup analysis was consistent with the main result and the rosacea population tended to have an increased risk for CVD compared with the reference population, albeit with attenuated statistical significance most likely because of the decreased number of cases upon stratification. Lastly, the treatment of rosacea was not considered. However, the first-line of rosacea treatment is mainly skin care, topical agents, devices and surgical therapies, and in moderate to severe cases, an oral agent is added.[49,50] The main oral agent used is a subantimicrobial dose of doxycycline, which is one quarter of the typical dose. It is well known that doxycycline does not raise the risk of CVD.[51] In addition, since doxycycline is also a commonly used drug in the management of several bacterial infections, sexually transmitted diseases, or inflammatory skin diseases, exposure to doxycycline in the reference group would not be uncommon.[52,53] Consequently, although the analysis did not consider rosacea treatment, this would not have a major impact on the results of this study.

Despite these limitations, our study has several strengths. First, we included multiple possible confounding variables of CVD, which is not consistent with previous studies. Second, we considered the temporal relationship between rosacea and CVD and consistent results in the sensitivity analysis and propensity score–matching support that rosacea might increase the risk for subsequent CVD. Third, our study included a large sample size with a long follow-up period. Lastly, a wide range of subgroup and sensitivity analyses enhances the generalizability and validity of the findings.

# CONCLUSIONS

In conclusion, patients with rosacea were more likely to have subsequent CVD. Proper education for patients with rosacea to manage other modifiable risk factors of CVD along with rosacea is needed.

### Affiliations

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## Disclosures

None.

## Supplementary Material

Tables S1–S3

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# SUPPLEMENTAL MATERIAL

**Table S1. Association of rosacea and cardiovascular disease with additional adjustments for diabetes, hypertension, and dyslipidemia medications.**

| | Reference population (n = 26,810) | Patients with rosacea (n = 2,681) | *P* value |
|---|---|---|---|
| **Cardiovascular disease** | | | |
| Events | 1,572 | 193 | |
| Incidence, per 1000 person-years | 9.36 | 11.44 | |
| aHR* (95% CI) | 1.00 (reference) | 1.24 (1.05-1.46) | 0.010 |
| **Coronary heart disease** | | | |
| Events | 731 | 99 | |
| Incidence, per 1000 person-years | 4.35 | 5.88 | |
| aHR (95% CI) | 1.00 (reference) | 1.36 (1.08-1.71) | 0.009 |
| **Stroke** | | | |
| Events | 913 | 103 | |
| Incidence, per 1000 person-years | 5.44 | 6.10 | |
| aHR (95% CI) | 1.00 (reference) | 1.13 (0.91-1.41) | 0.282 |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

*Adjusted hazard ratios were calculated by Cox proportional hazards regression after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, blood pressure, total cholesterol, fasting serum glucose, year of diagnosis, Charlson comorbidity index and diabetes, hypertension, and hyperlipidemia medications.

**Table S2. Baseline characteristics of the propensity score matched control.**

| | PS matched control (n = 2,642) | Patients with rosacea (n = 2,642) | Standardized difference |
|---|---|---|---|
| Age, years, mean (SD) | 57.3 (11.2) | 57.6 (9.2) | -0.028 |
| Sex, No. (%) | | | |
| Men | 1,396 (52.8) | 1,323 (50.1) | 0.055 |
| Women | 1,246 (47.2) | 1,319 (49.9) | |
| Household income, quartiles, No. (%) | | | |
| 1st (highest) | 1,249 (47.3) | 1,055 (39.9) | -0.012 |
| 2nd | 598 (22.6) | 733 (27.7) | |
| 3rd | 429 (16.2) | 477 (18.1) | |
| 4th (lowest) | 366 (13.9) | 377 (14.3) | |
| Smoking, No. (%) | | | |
| Never smoker | 1,829 (69.2) | 1,874 (70.9) | -0.037 |
| Past smoker | 545 (20.6) | 405 (15.3) | |
| Current smoker | 268 (10.1) | 363 (13.7) | |
| Physical activities, times/week, No. (%) | | | |
| 0 | 1,330 (50.3) | 1,239 (46.9) | -0.022 |
| 1-2 | 539 (20.4) | 587 (22.2) | |
| 3-4 | 332 (12.6) | 353 (13.4) | |
| ≥5 | 441 (16.7) | 463 (17.5) | |
| Alcohol intake, times/week, No. (%) | | | |
| 0 | 1,826 (69.1) | 1,782 (67.5) | 0.036 |
| 1-2 | 434 (16.4) | 543 (20.6) | |
| 3-4 | 251 (9.5) | 206 (7.8) | |
| ≥5 | 131 (5.0) | 111 (4.2) | |
| Charlson comorbidity index, No. (%) | | | |
| 0 | 1,038 (39.3) | 976 (36.9) | 0.048 |
| 1 | 638 (24.2) | 832 (31.5) | |
| ≥2 | 966 (36.6) | 834 (31.6) | |
| Body mass index, mean (SD), kg/m$^2$ | 23.7 (3.0) | 23.8 (2.8) | -0.056 |
| Systolic blood pressure, mean (SD), mmHg | 124.5 (15.5) | 124.6 (15.7) | -0.008 |
| Diastolic blood pressure, mean (SD), mmHg | 77.3 (10.2) | 77.7 (10.5) | -0.043 |
| Fasting serum glucose, mean (SD), mg/dL | 95.7 (22.0) | 97.9 (25.5) | -0.094 |
| Total cholesterol, mean (SD), mg/dL | 202.3 (37.8) | 199.9 (37.9) | 0.063 |
| Taking hypertension medication (%) | 817 (30.9) | 810 (30.7) | 0.006 |
| Taking diabetes medication (%) | 408 (15.4) | 421 (15.9) | -0.013 |
| Taking dyslipidemia medication (%) | 389 (14.7) | 452 (17.1) | -0.065 |

Abbreviations: PS, propensity score; SD, standard deviation.

**Table S3. Association of rosacea and cardiovascular disease by propensity score matching.**

| | PS matched control (n = 2,642) | Patients with rosacea (n = 2,642) | *P* value |
|---|---|---|---|
| **Cardiovascular disease** | | | |
| Events | 163 | 188 | |
| Incidence, per 1000 person-years | 9.58 | 11.26 | |
| aHR* (95% CI) | 1.00 (reference) | 1.30 (1.05-1.61) | 0.018 |
| **Coronary heart disease** | | | |
| Events | 80 | 95 | |
| Incidence, per 1000 person-years | 4.70 | 5.69 | |
| aHR (95% CI) | 1.00 (reference) | 1.30 (0.86-1.77) | 0.094 |
| **Stroke** | | | |
| Events | 92 | 102 | |
| Incidence, per 1000 person-years | 5.41 | 6.11 | |
| aHR (95% CI) | 1.00 (reference) | 1.31 (0.97-1.75) | 0.074 |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; PS, propensity score.
*Adjusted hazard ratios were calculated by Cox proportional hazards regression after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, blood pressure, total cholesterol, fasting serum glucose, year of diagnosis, and Charlson comorbidity index.